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Solid medical compsn. having improved disintegration - is prepd. from granules contg. at least two rarely water-soluble medicines

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Abstract (Basic): JP 8310969 A

Compsns. is prepd. from granules contg. 2 or more barely water soluble medicines, or 2 or more types of granules each contg. hardly water soluble medicine, water-swelling filler, one or more sugar components composed of sugars and sugar alcohols. Pref. barely water-soluble medicines has water solubility of 1 g/100 g or less at 30-40 deg.C. Water swelling fillers are pref. of crystalline cellulose, partially substd. hydroxypropylcellulose (HPC), carboxymethylcellulose (CMC), calcium CMC, crosslinked sodium CMC, carboxymethylethylcellulose and/or poylvinylpyrrolidone (PVP).

ADVANTAGE - Prepns. have improved disintegration. In an example, a tablet compsn. contg. 300 pts. of mefenamic acid, 30 pts. each of allylisopropylacetylurea and crystalline cellulose, 13 pts. of HPC, 15 pts. of mannitol and 2 pts. of Mg stearate, exhibited disintegration time of 2.4 minutes. While, conventional tablets showed disintegration time of 13.2 minutes or longer.

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(54)[Title of the invention] Solid pharmaceutical composition and process for preparing the same

[Claims]

[Claim 1] A solid pharmaceutical composition, which comprises a granule containing slightly water-soluble 2 or more granules each containing a slightly water-soluble drug, with a water-swelling excipient and 1 or 2 or more sugar ingredients selected from sugars and sugar alcohols incorporated.

[Claim 2] The solid pharmaceutical composition according to claim 1, wherein the slightly water-soluble drug has the solubility in water at 30 to 40°C of 1 (g/100 g water) or smaller.

[Claim 3] The solid pharmaceutical composition according to claim 1 or 2, wherein the water-swelling excipient is 1 or 2 or more selected from crystalline cellulose, slightly substituted hydroxypropylcellulose, carboxymethylcellulose, potassium carboxymethylcellulose, cross-linked sodium carboxymethylcellulose, carboxymethylethylcellulose and cross-linked polyvinyl pyrrolidone.

[Claim 4] A process for a preparing a solid pharmaceutical composition, which comprises incorporating a water-swelling excipient and 1 or more sugar ingredients selected from a sugar and a sugar alcohol, into a granule containing slightly

water-soluble 2 or more drugs or 2 or more granules each containing a slightly water-soluble drug.

[Detailed description of the invention]

[0001]

[Industrial field of utilization] The present invention relates to a solid pharmaceutical composition and a process for preparing the same, more particularly, a solid pharmaceutical composition even containing slightly water-soluble 2 or more drugs, which exhibit the excellent disintegrating property as well as a process for preparing the same.

[0002]

[Prior art and problems to be solved by the invention] When a solid pharmaceutical composition is prepared, generally, means to improve the absorbability in the living body and preparations aiming at improving easy administration are designed in many cases. In these solid pharmaceutical compositions, all ingredients of a composition are mixed, which is used as it is in some cases. However, in other cases, depending upon its use purpose, they are used as a tablet, a capsule or a granule. For example, when formulated into a granule, a dry-granulating method by adding an active ingredient and a suitable excipient and formulating with a roll compressor (JP-B45-15755), a wet-granulating method by

an extrusion granulator (JP-A 5-229936) and a method by treating with an water-soluble polymer compound using a fluidized granulator into a granule are adopted. The thus obtained granule or granule-like composition is adjusted to a constant particle diameter, thereafter, an additive is further added, this is compressed, which is used as a tablet, or a hard capsule or a divided agent which is filled with a constant amount of it is used.

[0003] However, when a subject drug has the low solubility in water, a solid pharmaceutical composition containing a drug which is granulated by the aforementioned granulating method is hardly disintegrated in the living body. In particular, in the case of a crystalline drug or a drug having a large particle diameter, a large amount of an excipient is necessary relative to a drug in order to maintain the better disintegrating property in the living body and this causes problems that an amount to be administered becomes large and the absorbalility of a drug itself is affected. As the strategy in this case, for example, a method in which a slightly water-insoluble drug is sufficiently finely divided, a surface area has an active ingredient for the drug is increased and, further, a binder is mixed therein in order to improve the absorbability and a method in which the affinity with water is improved by addition of a suitable surfactant,

for example, sucrose fatty acid ester, polyoxyethylene sorbitan fatty acid ester and the like, are used.

[0004] However, in a solid pharmaceutical composition in which slightly water-insoluble 2 or more drugs are incorporated, when the problem is tried to solve, for example, by mixing a finely-divided drug with a binder as the aforementioned method, since a binder is added directly to the surface of a slightly water-soluble drug (an impregnating liquid in the living body does not effectively act on these binding parts), the sufficient disintegrating ability can not be imparted to the whole composition. On the other hand, when a surfactant is added as in the latter method, the affinity with water is improved. However, the disintegrating ability of the whole composition can not be fundamentally solved due to the physical inhibition of a binder at an interface between granules.

[0005] The present invention was done in view of the above circumstances, and an object thereof is to provide a solid pharmaceutical composition containing slightly water-soluble 2 or more drugs, which has the improved disintegrating property, as well as a process for preparing the same.

[0006]

[Means to solve the problems and action] The present inventors extensively studied in order to attain the aforementioned

object and, as a result, found that, in a solid pharmaceutical composition in which a plurality of slightly water-soluble drugs are incorporated, by adding a sugar ingredient such as a sugar and a sugar alcohol together with a water-swelling excipient to a granule containing those slightly water-soluble drugs, the disintegrating property is remarkably improved, which resulted in completion of the present invention.

[0007] That is, the present invention provides a solid pharmaceutical composition, which comprises a granule containing slightly water-soluble 2 or more granules each containing a slightly water-soluble drug, with a water-swelling excipient and 1 or 2 or more sugar ingredients selected from sugars and sugar alcohols incorporated, as well as a process for preparing the same. Herein, it is suitable that the water-swelling excipient is 1 or 2 or more selected from crystalline cellulose, slightly substituted hydroxypropylcellulose, carboxymethylcellulose, potassium carboxymethylcellulose, cross-linked sodium carboxymethylcellulose, carboxymethylethylcellulose and cross-linked polyvinyl pyrrolidone.

[0008] The present invention will be described in detail below. The solid pharmaceutical composition of present invention contains. as an essential ingredient, a granule containing

2 or more kinds of slightly water-soluble drugs, a water-swelling excipient, and a sugar ingredient comprising sugars or sugar alcohols.

[0009] The slightly water-soluble drug in the present invention has the not particularly limited solubility. When an active ingredient is a drug having the solubility in water at 30 to 40°C of 1 (g/100 g water) or smaller, the present invention is particularly useful. Examples of such the active ingredient include antipyretic, analgesic and anti-inflammatory agents such as ethenzamide, ibuprofen, tolufenamic acid, phenacetin, meganamic acid, flufenamic acid, fucrocoutanine, sasapyrine, ketophenylbutazone, phenylbutazone, alclofenac, fenbufen, metiazinic acid, ketoprofen, naproxen, flurbiprofen, pranoprofen, tinoridine hydrochloride as well as noscapine, allylisopropylacetylurea and the like. These are incorporated in a combination of 2 or more. Herein, a combination of these drugs is not particularly limited as long as drugs can be incorporated by combination in a normal preparation.

[0010] It is desirable that, regarding a particle size of these drugs, particle size distribution and apparent specific gravity are adjusted in view of the mixing property with other drugs to be combined. Generally, a particle diameter is suitably 1 to 500 μm, particularly 10 to 80 μm. When the

diameter is less than 1 μm, a particle is hardly dispersed uniformly in an excipient or other active ingredients in some cases. When the diameter exceeds 500 μm, an active ingredient is easily separated and segregated in some cases. Herein, in order to obtain a particularly uniform preparation, it is most preferable that a particle diameter of each drug is 10 to 80 μm as described above.

[0011] In the solid pharmaceutical composition of the present invention, a single granule in which 2 or more kinds of the aforementioned drugs are combined, and a mixture of 2 or more kinds of granules, each containing 2 or more kinds of the aforementioned drugs are used. As a method for granulation, the known methods can be adopted. For example, granulation can be performed by appropriatly selecting a fluidized granulation method, a roll compression method, an extrusion granulation method, a stirring granulation method and the like depending upon the purpose of a preparation. For example, the solid pharmaceutical composition of the present invention is formulated into a dosage form such as a tablet and a capsule, a granule is obtained by a fluidized granulation method or a roll compression method and, in this case, the effects of the present invention become particularly remarkable. On the other hand, when rapid disintegration of the solid pharmaceutical composition is mainly aimed, a granule is

obtained by a fluidized granulation method and, in this case, the granule, an excipient and a sugar ingredient such as a sugar and a sugar alcohol are assuredly contacted, being most suitable. Upon granulation of a drug, an excipient, a binder and a disintegrating agent may be appropriately added in such a range that is not harmful on the effect of the present invention, as necessary.

[0012] A particle diameter of the aforementioned granule is preferably 100 to 2000 μm, more preferably 350 to 1000 μm, particularly preferably 350 to 800 μm. When the particle diameter is less than 100 μm, the flowablity of a particle becomes insufficient, and conveyance, mixing, compression and the like in a post step are affected in some cases. When the particle diameter exceeds 200 μm, the content per one time use of a drug varies greatly, problems of separation and segregation of granules are caused in some cases.

[0013] An amount of the aforementioned drug to be incorporated variously different depending upon a kind of a drug, a combination of drugs, a dosage form, an application object and the like. In the normal preparation, a combination in which a total amount of one time use amounts of these drugs is 50 mg or greater has the particularly great effects of the present invention. Generally, it is preferable that an amount to be incorporated is 95% (% by weight, the same

hereinafter) or smaller, particularly 90% or smaller of the whole composition. When the amount exceeds 95%, it is difficult to obtain the sufficient disintegrating property in some cases.

[0014] A kind of the water-swelling excipient in the present invention is not particularly limited as long as an excipient is a polymer substance which is insoluble or swollen in water and is porous. Cellulose derivatives and cross-linked water soluble polymer compounds which are used as an excipient in the normal preparations are suitably used. Examples of such the excipient include crystalline cellulose, slightly substituted hydroxypropylcellulose (substitution degree 5.0 to 16.0), carboxymethylcellulose (for example, carmelose), potassium carboxymethylcellulose (for example, potassium carmelose), cross-linked sodium carboxymethylcellulose (for example, cross sodium carmelose), carboxymethylethylcellulose, cross-linked polyvinyl pyrrolidone (for example, cross povidone) and the like. Among them, cross-linked sodium carboxymethylcellulose such as cross sodium carmelose and the like and cross-linked polyvinyl pyrrolidone such as cross povidone and the like are particularly suitable.

[0015] A particle size of the water-swelling excipient is not particularly limited and is suitably 1 to 100 μm, particularly

5 to 30 μm. When the particle size is less than 1 μm, the effects of incorporation of an excipient are decreased due to aggregation of excipient particles. When the particle size exceeds 100 μm, it is difficult to obtain the sufficient disintegrating property in some cases. In addition, a shape of a water-swelling excipient is preferably such that an excipient retains a void having a magnitude to such a degree that particles of the sugars or sugar alcohols are included. The number of the void is greater, it is more preferable.

[0016] An amount of the aforementioned water-swelling excipient varies variously depending upon a dosage form, an application object and the like. Generally, it is preferable that the amount is 1 to 50%, particularly 3 to 45% of a total amount of the aforementioned 2 or more kinds of slightly water-soluble drugs. When the amount is less than 1%, it is difficult to sufficiently improve the disintegrating property of the solid pharmaceutical composition in some cases. When the amount exceeds 50%, an administration amount becomes greater, being not desirable. It is preferable that an amount to be incorporated relative to the whole composition is 0.5 to 40%, particularly 1 to 30% of the whole composition based on the similar reasons described above.

[0017] In the solid pharmaceutical composition of the present invention, 1 or 2 or more sugar ingredients selected from

sugars and sugar alcohols are added in addition to the aforementioned excipient. Herein, as sugars in the present invention, the known sugars which are normally added to a pharmaceutical can be used. Examples of such the sugars include lactose, lactose anhydride, sucrose, fructose, dextrose and the like. These may be used singly or in a combination of 2 or more. Among them, lactose and lactose anhydride have little influence under the wet conditions, being particularly preferable. In addition, as sugar alcohols in the present invention, the known sugar alcohols which are normally added to a pharmaceutical can be used. Examples of such the sugar alcohols include mannitol, sorbitol, xylitol and the like. These may be used singly or in a combination of 2 or more.

[0018] A particle size of the aforementioned sugar ingredient is not particularly limited but, generally, 1 to 800 μm, particularly 10 to 100 μm is suitably used. When the particle size is outside the aforementioned range, it is difficult to prepare a solid preparation by adding a sugar ingredient in some cases.

[0019] An amount of the aforementioned sugar ingredient to be incorporated varies variously depending upon a dosage form, an application object and the like. It is generally preferable that the amount to be incorporated is 0.5 to 40%,

particularly 1 to 30% of a total amount of the aforementioned 2 or more kinds of slightly water-soluble drugs. When the amount is less than 0.5%, it is difficult to sufficiently improve the disintegrating property of the solid pharmaceutical composition in some cases. When the amount exceeds 50%, an administration amount becomes greater, being not desirable. It is generally preferable that an amount to be incorporated relative to the whole composition is 0.1 to 35%, particularly 1 to 20% of the whole position based on the similar reasons as described above. In addition, it is preferable that a total of an amount of the aforementioned water-swelling excipient and that of a sugar ingredient is 1.5 to 90%, particularly 3 to 80% of a total amount of the aforementioned slightly water-soluble drugs. In addition, it is preferable that the total amount is 0.6 to 75%, particularly 2 to 50% of the whole composition. When a total amount of an amount of the water-swelling excipient and that of a sugar ingredient is in the aforementioned range, the effects of the present invention becomes particularly remarkable.

[0020] When the solid pharmaceutical composition of the present invention is prepared, first, a single granule containing 2 or more kinds of slightly water-soluble drugs, or a mixture of 2 or more kinds of granules, each containing

1 or more kinds of slightly water-soluble drugs, is prepared, a water-swelling excipient and a sugar ingredient are mixed therein and, then, which is granulated and compressed depending upon the final dosage form.

[0021] Upon granulation and compression, a disintegrating agent such as starch and the like, a binder such as hydroxypropylcellulose (substitution degree 53.4 to 77.5%), methylcellulose, gelatin, vinylpyrrolidone, partially gelatinized starch and the like, various corrigents, pigments and the like may be appropriately added in such the range that is not harmful on the effects of the present invention, as necessary.

[0022]

[Effects of the present invention]

According to the present invention, even in the case of a solid pharmaceutical composition containing 2 or more kinds of slightly water-soluble drugs, preparations having the better disintegrating property can be obtained by incorporating a small amount of an additive.

[0023]

[Examples] The present invention will be specifically explained by way of Examples and Comparative Examples but the present invention is not limited to the following Example.

[0024] As slightly water-soluble drugs used in the following

Examples and Comparative Examples, they were used by passing through the following sieve, respectively, in advance.

[0025]

Slightly soluble drug	Opening of a sieve through which a drug was passed (μm)
Mefenamic acid	150
Allylisopropylacetylurea	180
Ibuprofen	180
Ethenzamide	106
Alclofenac	150
Ketoprofen	150

[0026] [Example 1] Mefenamic acid and allylisopropylacetylurea were used as a slightly water-soluble drug, they were subjected to fluidized granulation, mannitol and crystalline cellulose were added, which was compressed.

[0027] That is, 1500 g of mefenamic acid and 150 g of allylisopropylacetylurea were placed in a fluidized granulator (WSG-5 type: manufactured by Okawara), a binder solution obtained by dissolving 100 g of hydroxypropylcellulose (substitution degree 65%) in 2000 g of water in advance was sprayed to the predetermined amount of the following composition, to obtain a granule. To 343 parts (part by weight, the same hereinafter) of the aforementioned granule which had been classified using a 1400

μm sieve were added 30 parts of crystalline cellulose and 15 parts of mannitol, they were mixed for 10 minutes using a V-type mixer, 2 parts of magnesium stearate was further added and mixed for 3 minutes, which was compressed at a compression pressure of 1.2 t/cm^2 with a rotary-type compressing machine (L-41: manufactured by Hatatetsuko) to obtain a go-stone typed tablet of the following composition having a tablet weight of 390 mg and a diameter of 10 mm.

Composition

Mefenamic acid	300 parts
Allylisopropylacetylurea	30 parts
Hydroxypropylcellulose (substitution degree 65%)	13 parts
Crystalline cellulose	30 parts
Mannitol	15 parts
Magnesium stearate	2 parts
Total	390 parts

[0028] [Example 2] Ibuprofen and allylisopropylacetylurea were used as a slightly water-soluble drug, they were subjected to fluidized granulation, sorbitol and crystalline cellulose were added, which was roll-compressed and classified to obtain a granule.

[0029] That is, 1000 g of ibuprofen, 200 g of allylisopropylacetylurea and 200 g of partially gelatinized

starch were placed in a fluidized granulator (WSG-5 type), and a binder solution obtained by dissolving 100 g of hydroxypropylcellulose (substitution degree 65%) in 2000 g of water in advance was sprayed to the predetermined amount of the following composition, to obtain a granule. 7 parts of crystalline cellulose, 5 parts of sorbitol and 0.2 part of Yellow No.5 aluminum lake were added to 147.8 parts of the aforementioned granule which had been classified using a 1400 μm sieve, they were mixed for 15 minutes using a V-type mixer, which was then subjected to dry granulation using an Alexander dry granulator (WP50N: manufactured by Matsuzakaboeki) and classified to obtain a granule having the following composition. This granule satisfied the specification of a granule described in Japanese Pharmacopoeia.

Composition

Ibuprofen	100	parts
Allylisopropylacetylurea	20	parts
Partially gelatinized starch	20	parts
Hydroxypropylcellulose (substitution degree 65%)	7.8	parts
Crystalline cellulose	7	parts
Sorbitol	5	parts
Yellow No. 5 aluminum lake	0.2	part
Total	173	parts

[0030][Comparative Example 1] Mefenamic acid and allylisopropylacetylurea were used as a slightly water-soluble drug, they were subjected to fluidized granulation, corn starch as a disintegrating agent and crystalline cellulose as an excipient were added, which was compressed.

[0031] That is, 1500 g of mefenamic acid and 150 g of allylisopropylacetylurea were placed in a fluidized granulator (WSG-5 type), and a binder solution obtained by dissolving 100 g of hydroxypropylcellulose (substitution degree 65%) in 2000 g of water in advance was sprayed to the predetermined amount of the following composition, to obtain a granule. 50 parts of crystalline cellulose and 30 parts of corn starch were added to 343 parts of the aforementioned granule which had been classified using a 1400 μm sieve, they were mixed for 10 minutes using a V-type mixer, 2 parts of magnesium stearate was further added, and mixed for 3 minutes, which was compressed at a compression pressure of 1.2 t/cm^2 with a rotary-type compressing machine (L-41) to obtain a go-stone typed tablet of the following composition having a tablet weight of 425 mg and a diameter of 10 mm.

Composition

Mefenamic acid	300 parts
Allylisopropylacetylurea	30 parts
Hydroxypropylcellulose	

(substitution degree 65%)	13 parts
Crystalline cellulose	50 parts
Corn starch	30 parts
Magnesium stearate	2 parts
Total	425 parts

[0032][Comparative Example 2] Mefenamic acid and allylisopropylacetylurea were used as a slightly water-soluble drug, they were subjected to fluidized granulation, and corn starch as a disintegrating agent and lactose as an excipient were added, which was compressed.

[0033] That is, 1500 g of mefenamic acid and 150 g of allylisopropylacetylurea were placed in a fluidized granulator (WSG-5 type), and a binder solution obtained by dissolving 100 g of hydroxypropylcellulose (substitution degree 65%) in 2000 g of water in advance was sprayed to the predetermined amount of the following composition. 50 parts of lactose and 30 parts of corn starch were added to 343 parts of the aforementioned granule which had been classified using a 1400 μm sieve, they were mixed for 10 minutes using a V-type mixer, 2 parts of magnesium stearate was further added, and mixed for 3 minutes, which was compressed at a compression pressure of 1.2 t/cm^2 with a rotary-type compressing machine (L-41) to obtain a go-stone typed tablet of the following composition having a tablet weight of 425 mg and a diameter

of 10 mm.

Composition

Mefenamic acid	300 parts
Allylisopropylacetylurea	30 parts
Hydroxypropylcellulose (substitution degree 65%)	13 parts
Lactose	50 parts
Corn starch	30 parts
Magnesium stearate	2 parts
Total	425 parts

[0034] [Comparative Example 3] Ibuprofen and allylisopropylacetylurea were used as a slightly water-soluble drug, they were subjected to fluidized granulation, lactose and hydroxypropylstarch were added, which was roll-compressed and classified to obtain a granule.

[0035] That is, 1000 g of ibuprofen, 200 g of allylisopropylacetylurea and 200 g of partially gelatinized starch were placed in a fluidized granulator (WSG-5 type), and a binder solution obtained by dissolving 100 g of hydroxypropylcellulose (substitution degree 65%) in 2000 g of water in advance was sprayed to the predetermined amount of the following composition, to obtain a granule. 10 parts of lactose, 15 parts of hydroxypropylstarch and Yellow No.5 aluminum lake were added to 147.8 parts of the aforementioned

granule which had been classified using a 1400 μm sieve, they were mixed for 15 minutes using a V-type mixer, dry-granulated using an Alexander dry-granulator WP50N and classified to obtain a granule having the following composition. This granule satisfied the specification of a granule described in Japanese Pharmacopoeia.

Composition

Ibupropfen	100	parts
Allylisopropylacetylurea	20	parts
Partially gelatinized starch	20	parts
Hydroxypropylcellulose (substitution degree 65%)	7.8	parts
Lactose	10	parts
Hydroxypropylstarch	15	parts
Yellow No.5 aluminum lake	0.2	part
Total	173	parts

[0036] [Comparative Example 4] Ibuprofen and allylisopropylacetylurea were used as a slightly water-soluble drug, partially gelatinized starch was added, they were subjected to fluidized granulation, carboxymethylcellulose and Yellow No.5 aluminum lake were added, which was roll-compressed and classified to obtain a granule.

[0037] That is, 1000 g of ibuprofen, 200 g of

allylisopropylacetylurea and 200 g of partially gelatinized starch were placed in a fluidized granulator (WSG-5 type), and a binder solution obtained by dissolving 100 g of hydroxypropylcellulose (substitution degree 65%) in 2000 g of water in advance was sprayed to the predetermined amount of the following composition, to obtain a granule. 25 parts of partial carboxymethylcellulose and 0.2 part of Yellow No.5 aluminum lake were added to 147.8 parts of the aforementioned granule which had been classified using a 1400 μm sieve, they were mixed for 15 minutes using a V-type mixer, dry-granulated using an Alexander dry granulator WP50N and classified to obtain a granule having the following composition. This granule satisfied a granule described in Japanese Pharmacopoeia.

Composition

Ibuprofen	100	parts
Allylisopropylacetylurea	20	parts
Partially gelatinaized starch	20	parts
Hydroxypropylcellulose (substitution degree 65%)	7.8	parts
Carboxymethylcellulose	25	parts
Yellow No.5 aluminum lake	0.2	part
Total	173	parts

[0038] [Comparative Example 5] Mefenamic acid and

allylisopropylacetylurea were used as a slightly water-soluble drug, mannitol and crystalline cellulose were added to them, powders were mixed, they were subjected to fluidized granulation, magnesium stearate was added, which was compressed.

[0039] That is, 150 parts of crystalline cellulose and 75 parts of mannitol were added to 1500 g of mefenamic acid and 150 g of allylisopropylacetylurea, they were mixed for 10 minutes using a V-type mixer, which was placed in a fluidized granulator (WSG-5 type), and a binder solution obtained by dissolving 100 g of hydroxypropylcellulose (substitution degree 65%) in 2000 g of water in advance was sprayed to the predetermined amount of the following composition, to obtain a granule. 2 parts of magnesium stearate was added to 388 parts of the aforementioned granule which had been classified using a 1400 μm sieve, they were mixed for 10 minutes using a V-type mixer, which was compressed at a compression pressure of 1.2 t/cm^2 with a rotary-type compression machine (L-41) to obtain a go-stone typed tablet of the following composition having a tablet weight of 390 mg and a diameter of 10 mm.

Composition

Mefenamic acid	300 parts
Allylisopropylacetylurea	30 parts
Hydroxypropylcellulose	

(substitution degree 65%)	13 parts
Crystalline cellulose	30 parts
Mannitol	15 parts
Magnesium stearate	2 parts
Total	390 parts

[0040] Regarding respective pharmaceutical compositions of Examples 1 and 2 and Comparative Examples 1 to 5, a disintegrating time was measured according to a disintegrating test method described in Japanese Pharmacopoeia. The results are shown in Table 1. The test was performed using a disintegrating test machine (manufactured by Toyama Sangyo) according to Japanese Pharmacopoeia and, as a test solution, the first solution was used.

[0041]

[Table 1]

	Dosage form	Disintegrating time (min.)
Example 1	Tablet	2.4
Comparative Example 1	Tablet	13.2
Comparative Example 2	Tablet	14.8
Comparative Example 5	Tablet	>15
Example 2	Granule	1.3
Comparative Example 3	Granule	15.5
Comparative Example 4	Granule	18.7

[0042] According to the results in Table 1, in the solid

pharmaceutical composition of the present invention, whether the dosage form is tablet or granule, a disintegrating time is remarkably shortened, respectively, while when only a water-swelling excipient is added (Comparative Examples 1 and 4), when only a sugar ingredient is added (Comparative Examples 2 and 3) and when a water-swelling excipient and a sugar ingredient are added in the state where a drug is not formulated into a granule (Comparative Example 5), regardless of a dosage form, it is recognized that a disintegrating time is hardly shortened in any case. In addition, it is recognized that, in the solid pharmaceutical composition of the present invention, whether tablet or granule, a disintegrating time is shortened even when an amount of an excipient is small.

[0043] Accordingly, in the case of the solid pharmaceutical composition of the present invention, it was confirmed that, when a water-swelling excipient is added alone, or a sugar ingredient is added alone, the effects are not recognized and when both are present, the remarkable synergistic effects are recognized.

[0044] In order to examine the influence of a total amount of a water-swelling excipient and a sugar ingredient to be corporated, tablets were prepared by the same preparation method as that of Example 1 according to the composition shown

in Table 2, and a disintegrating time of each tablet was measured as described above. The results thereof are also shown in Table 2.

[0045]

[Table 2]

Ingredient	Test Example		
	1	2	3
Mefenamic acid	300 parts	300 parts	300 parts
Allylisopropylacetylurea	30 parts	30 parts	30 parts
Hydroxypropylcellulose (substitution degree 65%)	13 parts	13 parts	13 parts
Crystalline cellulose	30 parts	15 parts	10 parts
Mannitol	15 parts	8 parts	4 parts
Magnesium stearate	2 parts	2 parts	2 parts
Total	390 parts	368 parts	359 parts
Ratio of a total weight of a water-swelling excipient and a sugar ingredient relative to weight of a drug	13.6% by weight	7.0% by weight	4.2% by weight
Ratio of a total amount of drugs of a water-swelling excipient and a sugar ingredient relative to weight of a drug	11.5% by weight	6.3% by weight	3.9% by weight
Disintegrating time	2.4 min.	5.5 min.	10.5 min.

[0046] According to the results in Table 2, it is recognized that, in the case of the above Test Example, when a total amount of a water-swelling excipient and a sugar component to be incorporated is 4% of a total of a total amount of drugs to be incorporated and 4% relative to the whole composition, the disintegrating property is improved and, when a total amount of drugs to be incorporated is 7% or greater and 6% or greater relative to the whole composition, the effects are

particularly remarkable.

[0047][Example 3] Ethenzamide and allylisopropylacetylurea were used as a slightly water-soluble drug, they were subjected to fluidized granulation, mannitole and cross povidone were added, which was compressed.

[0048] That is, 2500 g of ethenzamide and 300 g of allylisopropylacetylurea were placed in a fluidized granulator (Spiraflow type), and a binder solution obtained by dissolving 120 g of polyvinyl pyrrolidone (K30) in 2000 g of water in advance was sprayed to the predetermined amount of the following composition, to obtain a granule. 30 parts of anhydrous caffeine, 100 parts of acetaminophen, 20 part of cross povidone and 10 parts of mannitol were added, they were mixed for 20 minutes using a V-type mixer, 3 parts of magnesium stearate was further added, and mixed for 3 hours, which was compressed with a rotary-type compressing machine (Clean press) to obtain a football-type tablet of the following composition having a tablet weight of 456 mg, a long diameter of 17 mm and a short diameter of 7 mm. A disintegrating time of this tablet was measured as described above and found to be 1.7 minutes.

Composition

Ethenzamide	250 parts
Allylisopropylacetylurea	30 parts

Polyvinyl pyrrolidone K30	13 parts
Anhydrous caffeine	30 parts
Acetaminophen	100 parts
Cross povidone	20 parts
Mannitol	10 parts
Magnesium stearate	3 parts
Total	456 parts

[0040][Example 4] Alclofenac, ethenzamide and allylisopropylacetylurea were used as a slightly water-soluble drug, they were subjected to fluidized granulation, potassium carboxymethylcellulose and mannitol were added, which was compressed.

[0050] That is, 500 g of alclofenac, 500 g of ethenzamide and 300 g of allylisopropylacetylurea were placed in a fluidized granulator (spiraflow type), and a binder solution obtained by dissolving 120 g of polyvinyl pyrrolidone (K30) in 2000 g of water in advance was sprayed to the predetermined amount of the following composition, to obtain a granule. 25 parts of anhydrous caffeine, 20 parts of potassium carboxymethylcellulose and 20 parts of mannitol were added to 133 parts of the aforementioned granule which had been classified using a 1400 μm sieve, they were mixed for 20 minutes using a V-type mixer, 2 parts of magnesium stearate was further added, and mixed for 3 minutes, which was

compressed with a rotary-type compressing machine (Clean press) to obtain a round-type tablet of the following composition having a tablet weight of 190 mg and a diameter of 7 mm. A disintegrating time of this tablet was 1.6 minutes.

Composition

Alclofenac	50 parts
Ethenzamide	50 parts
Allylisopropylacethylurea	30 parts
Polyvinyl pyrrolidone K30	3 parts
Anhydrous caffeine	25 parts
Potassium carboxymethylcellulose	20 parts
Mannitol	10 parts
Magnesium stearate	2 parts
Total	190 parts

[0051] [Example 5] Ketoprofen and allylisopropylacetylurea were used as two kinds of slightly water-soluble drugs, they were subjected to fluidized granulation, mannitol, potassium carboxymethylcellulose and crystalline cellulose were added to obtain a granule, which was filled in a capsule to obtain a capsule.

[0052] That is, 500 g of ketoprofen and 300 g of allylisopropylacetylurea were placed in a fluidized granulator (Spiraflow-type), a binder solution obtained by dissolving 100 g of polyvinyl pyrrolidone (K30) in 2000 g of

water in advance was sprayed to the predetermined amount of the following composition, to obtain a granule. 20 parts of potassium carboxymethyl cellulose, 10 parts of crystalline cellulose and 20 parts of mannitol were added to 133 parts of the aformentioned granule which had been classified using a 850 μm sieve, they were mixed for 20 minutes using a V-type mixer, thereafter, which was dry-granulated by a roll compression method, 2 parts of magnesium stearate was further added, mixed for 3 minutes, which was filled in a No.2 hard capsule to obtain a hard capsule having the following composition. A disintegrating time of this capsule is 2.8 minutes.

Composition

Ketoprofen	50 parts
Allylisopropylacetylurea	30 parts
Polyvinyl pyrrolidone K30	3 parts
Potassium carboxymethylcellulose	20 parts
Crystallne cellulose	10 parts
Mannitol	20 parts
Magnesium stearate	2 parts
Total	135 parts

[0053] [Example 6] Ethenzamide and allylisopropylacetylurea were selected as a slightly water-soluble drug, they were individually subjected to fluidized granulation, mannitol

and cross povidone were added, which was compressed.

[0054] That is, 2000 g of ethenzamide was placed in a fluidized granulator (Spiraflow-type), a binder solution obtained by dissolving 100 g of polyvinyl pyrrolidone (K30) in 2000 g of water in advance was sprayed to the predetermined amount of the following composition, to obtain a granule. Then, 300 g of allylisopropylacetylurea was granulated with a desk-top fluidized granulator, each granule was classified using a 1000 μm sieve, 30 parts of anhydrous caffein, 100 parts of acetaminophen, 20 parts of cross povidone and 10 parts of mannitol were added to 243 parts of a mixed granule obtained by mixing respective granules at a mixing ratio of 20:30 using a V-type mixer, they were mixed for 20 minutes using a V-type mixer, 3 parts of magnesium stearate was further added, and mixed for 3 minutes, which was compressed with a rotary-type granulolator (Clean press) to obtain a football-type tablet of the following composition having a tablet weight of 406 mg, a long diameter of 16 mm and a short diameter of 6 mm. A disintegrating time of this tablet if 1.3 minutes.

Composition

Ethenzamide	200	parts
Polyvinyl pyrrolidone K30	11.3	parts
Allylisopropylacetylurea	30	parts

Polyvinyl pyrrolidone (K30)	2.7	parts
Anhydrous caffein	30	parts
Acetaminophen	100	parts
Cross povidone	20	parts
Mannitol	10	parts
Magnesium stearate	3	parts
Total	406	parts

[0055][Example 7] Ketoprofen and allylisopropylacetylurea were selected as a slightly water-soluble drug, they were subjected to dry-granulated by a roll compression method, mannitol, potassium carboxymethylcellulose and slightly substituted hydroxypropylcellolose (substitution degree 10.5%) were added and formulated into a granule, which was filled in a capsule to obtain a capsule.

[0056] That is, 50 parts of lactose was added to 500 g of ketoprofen and 200 g of allylisopropylacetylurea, they were uniformly mixed with a V-type mixer, dry-granulated with a roll-type granulator (roller compactor-type), to obtain a granule. To 75 parts of this granule were added 20 parts of potassium carboxymethylcellulose, 10 parts of slightly substituted hydroxypropylcellulose (substitution degree 10.5%) and 20 parts of mannitol, they were mixed for 20 minutes using a V-type mixer, dry-granulated by a roll compression method to obtain a granule, this granule was classified using

a 850 μm sieve to obtain a granule, and to 125 parts of granule was added 5 parts of hydrogenated castor oil, they were mixed for 3 minutes, which was filled in a No.2 hard capsule to obtain a hard capsule of the following composition. A disintegrating time of this capsule was 5.5 minutes.

Composition

Ketoprofen	50 parts
Allylisopropylacetylurea	20 parts
Lactose	5 parts
Potassium carboxymethylcellulose	20 parts
Slightly substituted hydroxypropylcellulose substitution degree 10.5%)	10 parts
Mannitol	20 parts
Hydrogenated castor oil	5 parts
Total	130 parts

(57) [Abstract]

[Construction] A solid pharmaceutical composition, which comprises a granule containing slightly water-soluble 2 or more granules each containing a slightly water-soluble drug, with a water-swelling excipient and 1 or 2 or more sugar ingredients selected from sugars and sugar alcohols incorporated.

[Effects] Even in the case of a solid pharmaceutical composition containing slightly water-soluble 2 or more drugs, a preparation having the better disintegrating property can be obtained by incorporating an additive at a small amount.